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Design and Synthesis of Sugar-modified Triazole-linked Dinucleosides

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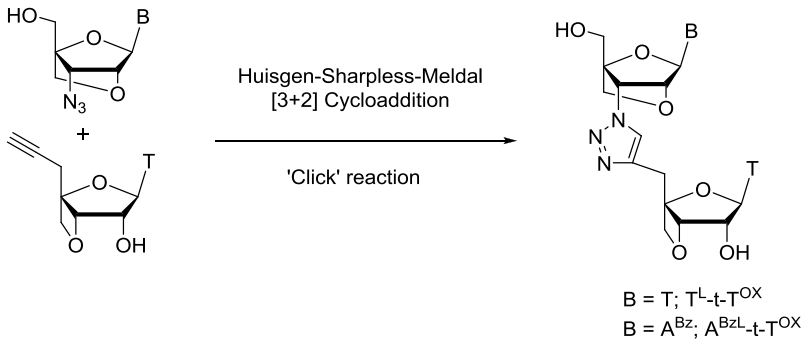
Abstract



Two sugar-modified triazole-linked nonionic dinucleosides T^{L}-t-T^{OX} and A^{BzL}-t-T^{OX} have been designed and synthesized by Cu(I)-catalyzed Huisgen-Sharpless-Meldal [3+2] cycloaddition reaction of 5′-deoxy-5′-*C*-ethynyl-3′-*O*,4′-*C*-methylene-ribothymidine with 3′-azido-3′-deoxy-2′-*O*,4′-*C*-methylenethymidine and 3′-azido-3′-deoxy-2′-*O*,4′-*C*-methylene-6-*N*-benzoyladenosine in 93% and 87% yields. Among the two Cu(I) reagents used for click reaction, $CuSO_4.5H_2O$-sodium ascorbate was found to be better yielding than $CuBr.SMe_2$. The cyclic and rigid triazole linkage is very hard to accommodate between the nucleotides without huge perturbation in the duplex nucleic acid structures. Therefore, the triazole-linked oligonucleotides have low binding affinity for the complementary nucleic acids. The Locked nucleic acid (LNA) and oxetane-sugar could provide a combination of different sugar puckers which can accommodate triazole linkage without compromising the binding affinity.

Keywords: Click-chemistry, Sugar modification, Locked nucleic acid, Triazole linkage.

1. Introduction

In the quest of potential antisense and antigene drug candidates, numerous backbone and/or sugar modifications of DNA/RNA have been reported.[1-6] It is due to the advantages of copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction, the synthesis of triazole-linked dinucleoside/oligonucleotides have been successfully achieved containing 3 to 6 atoms in the internucleotide residue (**1b-h**, Figure 1).[7-10]

Mainly two designs of triazole backbone have been explored in place of phosphate in oligonucleotides (Figure 1). The six-atom triazole linkage **1b** has been studied in detail by Brown et al.[11-15] This triazole linkage is biocompatible and can be read by DNA and RNA polymerases as natural substrate.[12] However, this triazole linkage tend to destabilise the duplex towards complementary DNA/RNA (ΔT_m = ~ -4-8 ºC/modification).[13] This triazole linkage in combination with other high affinity modifications such as G-clamp[14] or locked nucleic acid (LNA, **1d**)[15] can have improved binding affinity depending on the oligonucleotide sequence.

The second four-atom triazole linkage **1c** (Figure 1) was given by Isobe et al in 2008.[16-18] A fully triazole-linked decamer was synthesized using the Cu(I) catalysed click reaction. Interestingly this neutral decamer has high binding affinity for the complementary DNA.[18] When this linkage was partially inserted as dinucleoside blocks in oligonucleotides **1e**, low binding affinity was observed (ΔT_m = ~ -8 ºC/modification).[19-20] Nevertheless this linkage has been successfully incorporated in antisense oligonucleotides (ASOs) by Isobe et al.[16,17]

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"**This manuscript is dedicated to (Late) Prof. Naval Kishore Mathur, Former President, ACCT(I) for his extraordinary contribution in the area ofGalactomannan."**